IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:) : Examiner: Mojdeh Bahar

WOLFGANG HEIL ET AL.) : Group Art Unit: 1617

Application No.: 09/654,227) :

Filed: August 31, 2000) :

For: **PHARMACEUTICAL COMPOSITION FOR USE AS A CONTRACEPTIVE**

Hon. Commissioner of Patents and Trademarks
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.132
OF HERMAN ELLMAN

Sir:

I, Herman Ellman, residing at 2 Cliffside Way, Boonton Township, NJ 07005, do hereby declare and say that:

I. Introduction

1. I received a M.D. degree in Medicine from SUNY Downstate in 1972.

2. I was employed by Berlex Laboratories Inc. ("Berlex"), a U.S. affiliate of Schering Aktiengesellschaft, Germany ("Schering AG"), the assignee of the above-identified patent application, from October 1988 until June 2000, and was involved in managing clinical trials at Berlex for the entire duration of my employment.

3. I have read the specification of the above-identified patent application, including the presently claimed subject matter, and understand that it encompasses the active pharmaceutical composition used in Berlex's clinical study project, Protocol 96049, titled "An Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of a Monophasic Oral Contraceptive Preparation, Containing Drospirenone 3 mg and Ethinyl Estradiol 30 µg" (the "Clinical Study"). A copy of the Protocol for this Clinical Study is attached as Exhibit A to the attached Information Disclosure Statement.[1/] I was the Study Manager of that project from its inception in 1996 until its completion in 1998. As Study Manager, I had full control, subject only to upper management approval, of designing, implementing and overseeing this clinical study.

II. The Active PharmaceuticalComposition Used in the Clinical Study

4. It is my understanding that the above-identified patent application describes and claims pharmaceutical compositions comprising the active ingredients, drospirenone and ethinylestradiol, in micronized form. Therefore, this application encompasses the active pharmaceutical composition used in the Clinical Study (the "Clinical Study Drug").

1/ I understand this Protocol was initially designated as number "96049," but because of two minor revisions, was subsequently designated "96049A" and "96049B."

III. No Public Use, Offer for Sale or Sale of the Active Pharmaceutical Composition Occurred Prior to at Least August 31, 1998

5. I have read the attached Information Disclosure Statement, including the Exhibits cited in it, which refer to the activities of Berlex prior to the August 31, 1999, filing date of the above-identified patent application.

6. I have been informed that August 31, 1998, which is one year prior to the first-filed United States application, is an important date because certain types of activities that occurred more than one year prior to this filing date may have bearing on patentability. Specifically, I have been informed that using an invention publicly, offering it for sale or selling it more than one year prior to the filing date of a patent application can destroy the right to obtain a patent.

7. To my knowledge and on my belief, no one within Berlex, Schering AG or any third parties involved in the Clinical Study publicly used the Clinical Study Drug prior to August 31, 1998. The activities concerning the Clinical Study were confidential, closely monitored by Berlex and conducted for the experimental purpose of determining the efficacy and safety of the Clinical Study Drug. In fact, the Clinical Study was part of Berlex's Investigational New Drug Application ("IND") to the U.S. Food and Drug Administration ("FDA"), as the Clinical Study Drug required further investigation, experimentation and development as of August 31, 1998. To accomplish this, Berlex needed the assistance and expertise of Clinical Investigators, Institutional Review Boards, study patient volunteers and other clinical support staff and services.

8. In addition, the Clinical Study Drug was not offered for sale or sold prior to at least August 31, 1998. The Clinical Study Drug was not offered for sale or sold

at any time during the Clinical Study. In fact, Berlex provided the Clinical Study Drug free to patients in the Clinical Study, and even provided free medical care and compensation to the patients in the Clinical Study:

> Compensation for you for study participation include[s] free study medication, laboratory tests, Pap smears and physical examinations including breast and pelvic examinations.
>
> You will be paid $40.00 per visit up to a total of $240.00 for time and travel expenses. If you do complete the study, you will be paid for all completed visits.

(See Exhibit H, p. 7, "Patient Compensation").

9. Moreover, prior to August 31, 1998, Berlex never told any third parties involved in the Clinical Study of the micronized nature of the Clinical Study Drug.

IV. Berlex's Clinical Study Strategy

10. Because Berlex lacked the information needed to determine whether the Clinical Study Drug was safe and effective for its intended purpose, we had to design and implement an experimental program that would test subjects and yield data sufficient to make that determination. Only testing in humans, under actual use conditions, could determine whether the tested composition was safe and effective. This human testing, furthermore, could only be accomplished by recruiting third parties, such as contract research organizations, investigators and patient volunteers, to participate in the Clinical Study. In addition, because of the contraceptive action of the Clinical Study Drug, the Clinical Study was "open-label" and not placebo-controlled, meaning it was not conducted with blinding (i.e., where the investigators and patients are not informed of the ingredients

of the Clinical Study Drug), as it would have been unethical to have patients attempt to prevent or risk pregnancy without their consent.

11. Berlex's primary requirements for the Clinical Study were that the Clinical Investigators involved have the expertise needed for determining the safety and efficacy of the Clinical Study Drug, accept obligations of confidentiality concerning the Clinical Study and the Clinical Study Drug, adhere to the rules and requirements of Federal regulations and the Protocol of the Clinical Study, and work under Berlex's supervision. All requirements were met.

V. The Protocol of the Clinical Study

12. Over 300 patients from six Clinical Investigator sites participated in the Clinical Study. As explained in more detail below, the Clinical Investigators dealt directly with these patients, and Berlex regularly, continuously and closely monitored the Clinical Investigators and the test results.

13. A meeting was held with all the Clinical Investigators on November 10-11, 1996 (see Exhibit B in attached Information Disclosure Statement), to introduce and familiarize the Clinical Investigators with the Protocol for the Clinical Study. The Clinical Study closed in 1998.

VI. The Clinical Investigators

A. All Disclosures to the Clinical Investigators Were Confidential

14. Prior to August 31, 1998, six (6) Clinical Investigators received information regarding the Protocol for the Clinical Study from Berlex. In each case, the

Clinical Investigators signed letter agreements ("Agreement Letter") that required confidentiality before Berlex disclosed the Protocol and gave the Clinical Study Drug to the Investigators. See Exhibit C in the attached Information Disclosure Statement, for Agreement Letters for all six Clinical Investigators.

15. Berlex's agreement with each Clinical Investigator imposed a duty on that Investigator to keep any information concerning the Protocol and the Clinical Study Drug confidential. (See Exhibit C). The Agreement Letter also specifically prohibited the Clinical Investigators from disclosing any clinical trial information without Berlex's permission in order to preserve Berlex's intellectual property rights. The Agreement stated:

> For all publications or presentations, a manuscript of the paper or abstract must be reviewed by Berlex before outside submission. This procedure is necessary to prevent premature disclosure of trade secrets or otherwise patent-protected materials and is in no way intended to restrict publication of facts or opinions formulated by the Investigator.

(See Exhibit C, p. 2).

16. Berlex's objective in discussing the Protocol and the Clinical Study Drug with these Clinical Investigators was not to publicly disclose, publicly use or allow public disclosure or unrestricted, non-experimental, non-confidential use of the study drug, but rather, to attempt to gain their interest and persuade them to participate in the experimental Clinical Study in order to determine whether the Clinical Study Drug was safe and effective. To inform these Clinical Investigators about the Clinical Study, Berlex distributed, in addition to the Protocol, an Investigator's Brochure and Case Report Form ("CRF") to each Investigator (identified as Exhibits D and E, respectively, in the attached Information Disclosure Statement). Berlex marked the Protocol "CONFIDENTIAL" in

bold, capital type on the first page, (see Exhibit A, p. 1), and elaborated on the confidential nature of the clinical study in section 12.9, titled "Confidentiality":

> The Protocol, Case Report Form and Investigator's Brochure provided to you as a Principal Investigator for review by you, your staff and applicable Institutional Review Board(s), are confidential. It is understood that this information provided to you by Berlex Laboratories in connection with this study, must not be disclosed to others without written authorization from Berlex Laboratories, except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered.

(See Exhibit A, p. 28).

17. To emphasize the importance of confidentiality, Berlex also marked the Investigator's Brochure cover with a large "CONFIDENTIAL" designation and the following statement in capital letters:

> INFORMATION CONTAINED HEREIN IS FOR THE USE OF INVESTIGATORS ONLY AND MAY NOT BE REPRODUCED IN WRITING OR IN ORAL PRESENTATION WITHOUT THE PERMISSION OF BERLEX LABORATORIES, INC.

(See Exhibit D, cover page).

18. None of the information distributed to the Clinical Investigators described or disclosed the micronized form of the Clinical Study Drug.

B. Berlex Limited Distribution and Access to the Clinical Study Drug

19. Berlex restricted the experimental use of the Clinical Study Drug by enacting a number of drug access and accounting safeguards. One of those safeguards appeared in the Agreement Letter with the Clinical Investigators, where Berlex required each Investigator to undertake to keep the Clinical Study Drug in a secure location, restrict its access to patients enrolled in the Clinical Study, and maintain an accounting of the Clinical Study Drug and all other study materials:

By agreeing to participate, you will ensure that all study drugs are appropriately stored. None of the study drug(s) will be used for patients outside this protocol. When the study is completed there will be a full accounting of all study materials which will be audited by Berlex personnel.

(See Exhibit C, p. 1).

20. In section 12.1 of the Protocol, Berlex provided the Clinical Investigators with a detailed statement of their obligations concerning the Clinical Study Drug:

> All study drug used in this study will be supplied to the Principal Investigator by the Sponsor. Study drugs must be kept in an appropriate, secure area.
>
> The Principal Investigator must retain a copy of the receipt of test drug as shipped by the Sponsor, including the date received. The duplicate copy of this receipt must be returned to the Sponsor when the contents of the drug shipment have been verified. In addition, an accurate study drug dispensing record must be kept specifying the amount dispensed to each subject and the date of administration. This inventory record must be available for inspection by representatives of Berlex and is subject to FDA inspection at any time. A copy of this record must be provided to the Sponsor by the Principal Investigator at the conclusion of the study.
>
> Study drug is to be used only in accordance with this Protocol and under the supervision of the Principal Investigator.
>
> At the conclusion of this study, the Sponsor will provide instructions for the return of all study drug. All unused study drug, including opened and unopened labeled containers, must be returned to the Sponsor . . .

(See Exhibit A, p. 26).

21. Berlex further advised all Clinical Investigators that all aspects of the clinical study would be carefully and regularly monitored by Berlex representatives:

> All aspects of the study will be carefully monitored by representatives of Berlex Laboratories, who will review study documents with respect to current good clinical practices and for compliance with applicable government regulations. Particular attention will be paid to protocol variations, missing or incomplete data,

occurrence of serious or unusual adverse events or laboratory test abnormalities, appropriate investigational drug storage and signed informed consent.

(Exhibit A, p. 27, section 12.4, "Study Monitoring").

22. Not only did the Clinical Investigators agree to keep patients' Case Report Forms ("CRFs") confidential (see paragraph 16 above), but in the CRFs, the Investigators were required to keep track of the Clinical Study Drug dispensed to and returned by patients. See pages 7, 11, 15, 21, 25 and 31 of the CRF, identified as Exhibit E, and the Patient Tracking Sheet, Exhibit F in the attached Information Disclosure Statement.

23. Berlex also controlled access and availability of the Clinical Study Drug by requiring Investigators to complete a Drug Inventory Record (Exhibit G in the attached Information Disclosure Statement) for each patient. The Drug Inventory Record documented when and who dispensed the Clinical Study Drug, the quantity dispensed, when the patient returned the medication and the quantity returned. See the first six columns of the Drug Inventory Record, Exhibit G. Berlex further required its own staff to reconcile quantity of Clinical Study Drug dispensed and returned and to record the date the Clinical Investigators returned the Clinical Study Drug to Berlex. See the last two columns of the Drug Inventory Record, Exhibit G.

24. Beyond the study period, Berlex required the Clinical Investigators to keep all clinical study information, patient information and Clinical Study records confidential, and to store the information and records for at least 2 years, in compliance with Federal regulations. (See Exhibit A, p. 28, section 12.6, "Records Retention").

VII. The Clinical Study Patients

25. Berlex limited the number and defined the types of patients eligible to participate in the clinical study, and instructed each Clinical Investigator on the requirements for screening and enrolling patients for the clinical study. Berlex did not directly contact patients, but conveyed information about the clinical study through the Informed Consent document (see sample at Exhibit H, in the attached Information Disclosure Statement) and Patient Information leaflet (see Exhibit I, in the attached Information Disclosure Statement). The Informed Consent and Patient Information leaflet did not disclose to the patients or Clinical Investigators the micronized form of the Clinical Study Drug. Moreover, Berlex did not disclose this information to either the Clinical Investigators or the patients.

26. Additionally, the Informed Consent document explained that patient information would be kept confidential, except as required by law. (See Exhibit H, p. 7). This was another measure to guard against any non-confidential information disclosure.

27. As another control of the Clinical Study, Berlex dictated the manner in which patients were to account for the study drug throughout the study period. For example, Berlex also provided "Instructions for Use" of the Clinical Study Drug (Exhibit J in the attached Information Disclosure Statement), detailing step-by-step instructions on how and when to take the Clinical Study drug, and instructing patients to return all used, unused and partially used blister cards (packets containing the Clinical Study Drug). (See Exhibit J, second page). The Protocol also emphasizes that "[e]ach subject will also be instructed to return all used and unused medication packages at subsequent visits," (see Exhibit A, p. 12, section 5.4.4.1, "DRSP 3 mg/EE 30 µg Tablets"), and that "[a]t each visit,

all previously dispensed blister packs are to be returned to the investigator, even if they still contain drug" (see Exhibit A, p. 11, section 5.4.2, "Method of Dispensing").

VIII. The Contract Research Organizations

28. Because Berlex did not have the facilities or personnel necessary to perform clinical laboratory services for the Clinical Study, Berlex entered into an agreement with SciCor Inc., a contract research organization, to retain the required clinical laboratory services prior to initiation of the Clinical Study. See the Berlex-SciCor agreement, Exhibit K in the attached Information Disclosure Statement. SciCor undertook to "maintain the confidentiality of information and data . . . acquired about this clinical trial." (Exhibit K, p. 1).

29. Likewise, Berlex needed assistance in conducting monitoring services for the Clinical Study, and enlisted the help of another contract research organization, NCGS and Associates, Inc. ("NCGS"). NCGS agreed to perform monitoring services for Berlex and to keep confidential both Clinical Study-related and proprietary information:

> NCGS acknowledges and agrees that in the course of providing the Service as called for hereunder, NCGS may be exposed to or be given confidential or proprietary information of COMPANY ("Confidential Information"). NCGS agrees to hold all Confidential Information in secrecy during the term hereof and for ten (10) years thereafter. NGCS shall not disclose Confidential Information to third parties nor shall NCGS use such Confidential Information except in furtherance of this Agreement.

(See Exhibit L, p. 11, in the attached Information Disclosure Statement).

30. Because the Clinical Study Drug was still in an experimental, untested, unmarketed state as of August 31, 1998, and because the Clinical Study was

designed to determine the safety and efficacy of the Clinical Study Drug, Berlex needed the expertise of an Institutional Review Board ("IRB") to approve the Protocol, Patient Informed Consent and other clinical study materials and issues. Correspondingly, Berlex contracted Schulman Associates, an independent IRB. Like all other contract parties, Schulman Associates entered into an agreement that also governed confidentiality of study information.

IX. The Experimental Nature of the Clinical Study and the Clinical Study Drug

31. Not only was the Clinical Study confidential, controlled and closely monitored by Berlex, but it was also experimental in nature. The Protocol of the Clinical Study set forth the study objectives, namely, to evaluate "the safety and contraceptive efficacy of" the Clinical Study Drug. (See Exhibit A, p. 8). The Protocol specifically pointed out that the safety and effectiveness of the Clinical Study Drug had not yet been determined.

32. The Clinical Investigator's Brochure likewise emphasized the investigational, undetermined nature of the Clinical Study Drug, by stating in bold type:

> **This is an investigational drug, the efficacy of which has not yet been established.**

(See Exhibit D, p. 40).

33. Berlex also made all efforts through the Clinical Investigators to make certain that the Clinical Study patients were informed and reminded that the Clinical Study Drug was investigational and that the Clinical Study was to evaluate the Clinical

Study Drug. For example, in the "Nature and Purpose of the Study" section on the first page of the Informed Consent document, Berlex stated:

> This study is undertaken to examine the safety and effectiveness of an investigational (not yet approved by the U.S. Food & Drug Administration [FDA]) oral contraceptive preparation containing [the Clinical Study Drug].

(See Exhibit H, p. 1). Furthermore, the "Introduction" of the Patient Information leaflet, states in bold, all capital letters, that:

> **[THE CLINICAL STUDY DRUG] IS CURRENTLY BEING INVESTIGATED (THIS STUDY IS PART OF THE RESEARCH PROGRAM) AND ITS EFFECTIVENESS AS AN ORAL CONTRACEPTIVE HAS NOT YET BEEN ESTABLISHED.**

(See Exhibit I in the attached Information Disclosure Statement, at p. 1).

34. Berlex sought to measure both efficacy and safety variables to determine if the Clinical Study Drug was safe and effective. The primary efficacy variable was pregnancy rate (see Exhibit A, p. 18, section 6.2.1). Secondarily, effectiveness was evaluated by cycle control and intermenstrual bleeding (see Exhibit A, p. 18-19, section 6.2.1). Safety was assessed from "[t]reatment duration, vital signs, physical and pelvic exams, Pap smears, laboratory tests, and adverse events." (See Exhibit A, p. 19, section 6.2.2).

35. The Protocol instructed the Clinical Investigators to make safety and efficacy variable measurements and observations at predetermined intervals. (See Exhibit A, p. 13-17, section 5.5, "Measurement(s) and Observation(s)"). In addition, Investigators had to record each measurement and observation in each patient's Case Report Form, which would be returned to Berlex for data processing after completion of the study (see Exhibit A, p. 18, section 6.1, "Database Management Procedures").

36. Through the Clinical Investigators, Berlex also asked patients to complete daily Patient Diary cards to note any bleeding, pills taken or missed, and record other information, all in an effort to collect experimental data on the study drug's efficacy and safety. See Exhibit M in the attached Information Disclosure Statement. These diary cards eventually became part of each patient's CRF. (See Exhibit A, p. 16, section 5.5.3, "Subject Diaries").

* * *

37. As evidenced by the actions and information reported in the above paragraphs, Berlex's confidential disclosures of the study drug prior to August 31, 1998, were all directly related to Berlex's efforts to design, conduct and monitor an experimental Clinical Study that helped determine the safety and effectiveness of the Clinical Study Drug.

* * *

38. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true. In addition, all statements herein were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statement may jeopardize the validity of the application or any patent issuing thereon.

Subscribed this 28th day of NOVEMBER, 2003

Herman Ellman

NY_MAIN 380644v1